European Journal of Pharmaceutics and Biopharmaceutics 75 (2010) 225–231

Contents lists available at ScienceDirect

European Journal of Pharmaceutics and Biopharmaceutics

journal homepage: www.elsevier.com/locate/ejpb

Research paper

Transdermal fentanyl matrix patches Matrifen® and Durogesic® DTrans® are bioequivalent

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ARTICLE INFO

Article history:
Received 14 November 2009
Accepted in revised form 2 February 2010
Available online 10 February 2010

Keywords:
Bioequivalence
Fentanyl
Healthy subjects
Pharmacokinetics
Phase I
Pain
Opioid
Safety
Matrifen®
Durogesic® DTrans®

ABSTRACT

Aim: The pharmacokinetic profiles of the two commercially available transdermal fentanyl patches Matrifen® (100 μg/h) and Durogesic® DTrans® (100 μg/h), used to manage severe chronic pain, were compared regarding their systemic exposure, rate of absorption, and safety.
Methods: Transdermal matrix fentanyl patches [Matrifen® or Durogesic® DTrans® (100 μg/h)] were applied for 72 h to 30 healthy male subjects in a randomized, four-period (two replicated treatment sequences), crossover study; 28 subjects completed the study. The pharmacokinetic parameters of fentanyl were determined for 144 h after application using plasma samples. Safety of the patches (adverse events) and performance (adhesion, skin irritation, residual fentanyl content in the patch) were evaluated.
Results: The plasma concentration–time curves of Matrifen® (Test) and Durogesic® DTrans® (Reference) were similar. The geometric least square means of the Test/Reference ratio (90% confidence intervals [CI]) were within the range of 80–125%, demonstrating bioequivalence of Matrifen® and Durogesic® DTrans®: $AUC_{0\text{-tlast}}$ 92.5 (CI 88.7–96.4), $AUC_{0\text{-inf}}$ 91.7 (CI 88.0–95.7), and C_{max} 98.3 (CI 92.9–104.1). After 72 h application, Matrifen® had a more efficient utilization of fentanyl (mean ± SD 82.3 ± 9.43%) than Durogesic® DTrans® (52.3 ± 12.8%), with substantially lower residual fentanyl in patch after use. The pharmacokinetic parameters showed lower intra- and inter-subject variability for Matrifen® than for Durogesic® DTrans® patch.
Conclusions: Despite different technologies, the transdermal fentanyl patches Matrifen® and Durogesic® DTrans® are bioequivalent. Compared with Durogesic® DTrans®, the Matrifen® patch had lower initial and lower residual fentanyl content, as well as lower intra- and inter-subject variability, allowing reproducible drug delivery and reliable analgesia.

1. Introduction

Fentanyl is a highly potent, synthetic opioid with low molecular weight and high lipid solubility. These physicochemical properties make fentanyl a highly suitable agent for transdermal delivery [1]. Transdermal fentanyl is used for the management of severe chronic pain that can be controlled only by opioid analgesics. The efficacy of transdermal fentanyl in cancer and chronic non-cancer pain is well established [2], and several transdermal patches with different technologies (i.e. reservoir or matrix) are commercially available, although the market availability may differ in some countries.

Compared with other opioids, transdermal fentanyl has several advantages when used in appropriately selected patients with severe chronic cancer [3] and non-cancer pain [2,4]. Clinically relevant benefits include the ease of use for the patient, less interference with normal course of daily life [5], and less constipation [5–7]. Transdermal fentanyl is recommended for patients with renal failure/dialysis [8,9] and can be used in patients with renal or hepatic impairment [10], provided the respective safety parameters are clinically monitored.

The present European market leader Durogesic® DTrans® (Janssen-Cilag International NV, Beerse, Belgium) represents the *matrix* transdermal patch that was developed after the initial transdermal *reservoir* patch. The transdermal *reservoir* patch Durogesic® has

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doi:10.1016/j.ejpb.2010.02.005

been in use since the early 1990s but was associated with misuse and consequently discontinued [11]. To overcome such limitations, an alternative generation of transdermal *matrix* fentanyl patch was developed (Durogesic® DTrans® marketed in Germany under the name Durogesic® SMAT), in which the active drug is dissolved in a semi-solid polymer matrix [11–13]. More recently, an *advanced matrix* patch technology was developed (Matrifen®, Nycomed Roskilde, Denmark), consisting of fentanyl-containing dipropylene glycol droplets dispersed in a silicone matrix (Fig. 1). The Matrifen® patch contains a built-in rate-controlling membrane, which limits the diffusion of drug out of the matrix and ensures a constant release of fentanyl over the whole 72-h application period. The rate-controlling membrane improves the drug release and allows the initial drug load in the patch to be lower by at least 35% compared with Durogesic® DTrans® [14–18].

Both Matrifen® and Durogesic® DTrans® *matrix* patches have already been shown to be bioequivalent to the Durogesic® *reservoir* patch [16–18]. The objective of the present study in healthy subjects was to investigate the bioequivalence of the transdermal *matrix* patches Matrifen® and Durogesic® DTrans®, and to compare their safety, adhesiveness, and skin tolerability.

2. Materials and methods

2.1. Subjects and study design

The study was approved by the ethics committee (Medical Council Nordrhein, Düsseldorf, Germany) and performed at the clinical unit of ClinPharmCologne (MEDA Manufacturing GmbH, Cologne, Germany), according to the Declaration of Helsinki (Somerset West Amendment, 1996). In addition, during the conduct of the study the following specific guidelines were considered: note for guidance on the Investigation of Bioavailability and Bioequivalence (CPMP/EWP/QWP/1401/98) and note for guidance on Modified Release Oral and Transdermal Dosage Forms: Section II (Pharmacokinetic and Clinical Evaluation). Before entering the study, each subject gave written informed consent to participate in the trial.

A total of 30 healthy, male subjects were enrolled into the single-center, open label, single-dose, comparative, randomized, four-period, two-sequence, crossover, bioequivalence phase I study. The study protocol consisted of two replicated treatment sequences (periods 1–4). The washout interval between treatments was at least 11 days. All subjects were randomized to receive the patch formulations Matrifen® (treatment A) or Durogesic® DTrans® (treatment B), twice in a four-way crossover study according to the following sequences: ABAB and BABA. Subjects arrived at the clinical ward in the evening before the start of the study and were confined until 72 h after removal of the patch. To exclude a hidden opioid dependency, a naloxone challenge test was performed upon first admission to the ward.

The transdermal fentanyl patch was applied to the subject's non-dominant upper arm at 8 a.m. on day 1 of each study period and removed after a 72 h application period in the morning of day 4. During this time, standardized meals were served. To reduce potential receptor-mediated fentanyl-induced adverse events in the opioid-naive individuals, all subjects received two 50 mg tablets of naltrexone (Nemexin®) 1 h before patch application on day 1 and at the corresponding time points on days 2–6.

Matrifen® 100 μg/h (fentanyl) matrix transdermal patch was supplied by Nycomed (Roskilde, Denmark). Durogesic® DTrans® 100 μg/h, marketed in Germany under the name Durogesic® SMAT, transdermal patch was purchased from Janssen-Cilag (Beerse, Belgium). The surface area and fentanyl content for the transdermal patches are as follows: 33.6 cm^2, 11 mg for Matrifen® [15] and 42 cm^2, 16.8 mg for Durogesic® DTrans® [14].

2.2. Blood sampling and determination of drug concentrations

On the pharmacokinetic (PK) measurement days (days 1–7), serial blood samples were collected via vein-puncture or via an indwelling cannula, to measure the plasma concentrations of fentanyl after application of the transdermal patch. A total of 21 blood samples (4 mL at each time point) were taken during each treatment period at: pre-application, immediately *before* the patch application, and then *after* patch application at 6, 12, 18, 21, 24, 27, 30, 33, 36, 42, 48, 54, 60, 72, 84, 96, 108, 120, and 144 h. Blood was collected into EDTA-containing monovettes and immediately centrifuged at 1600*g*, 15 min, at +4 °C; plasma was transferred into plastic tubes within 60 min after collection and frozen at −20 °C or below until analysis.

2.3. Bioanalytical methods

Plasma concentrations of fentanyl were determined using a validated HPLC-MS/MS method (MDS Pharma Services, Fehraltdorf, Switzerland), which is a sensitive and specific method of liquid chromatography combined with mass spectrometry detection (LC/MS/MS) [16]. The assay was linear in the range between 0.01 μg L^{-1}

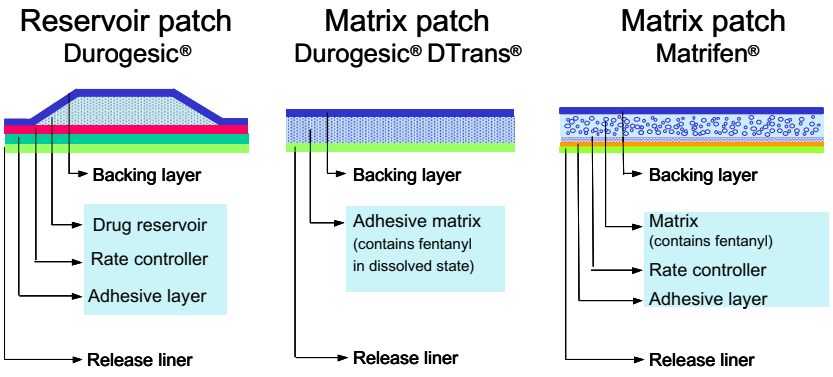

Fig. 1. Schematic presentation of transdermal patch technologies. The original Durogesic® patch, which is no longer available, contained fentanyl drug in a *reservoir*. Durogesic® DTrans®# and Matrifen® which were tested in the present study are currently commercially available. They represent advanced transdermal patches with fentanyl drug dissolved in a semi-solid *matrix*. The Matrifen® system contains a diffusion rate-controlling membrane that allows a controlled and constant rate of fentanyl release onto the skin through the skin into microcirculation providing for constant release without delivery surges or overdosing [10]. The surface area and fentanyl content for the transdermal patches are 33.6 cm^2, 11 mg for Matrifen® [15] and 42 cm^2, 16.8 mg for Durogesic® DTrans® [14]; the Matrifen® transdermal patch is 20% smaller than Durogesic® DTrans®. #Note: Durogesic® DTrans® is marketed in Germany under the trade name Durogesic® SMAT; apart from the trade name, the two products are identical.

and 2000 μg L^{-1}. The lower limit of quantification (LLOQ) for fentanyl was 0.01 μg L^{-1}. The inter-day precision (between-day coefficient of variation) ranged between 4.1% and 8.6%; the inter-day accuracy ranged between 103.7% and 108.4%. After removal of the transdermal patch, the residual fentanyl patch content was determined using a validated HPLC with ultraviolet detection based on a previously published method [19]. The nominal initial values of fentanyl were used for the calculation of the amount of fentanyl delivered to the subjects and the percentages of residual fentanyl in the used patches.

2.4. Safety investigations

Safety investigations included clinical laboratory tests (blood chemistry, haematology, urine analysis), physical examination, vital signs (blood pressure, pulse rate, and body temperature), and a resting standard 12-lead electrocardiogram (ECG) at the screening, day 1, day 4, and post-study examinations. Adverse events (AEs) were monitored throughout the study.

2.5. Skin irritation score

On days 4 and 5 (at 1, 12, and 24 h after patch removal), dermal response, (assessed as skin irritation) was evaluated according to the scoring system recommended by an FDA guidance [20]. The score system is based on a scale of 0–7, such that 0 = no evidence of irritation; one minimal erythema, barely perceptible; two definite erythema, readily visible; minimal edema or minimal papular/pustular response; three erythema and papules/pustules; 4 = definite edema; 5 = erythema, edema and papules; 6 = vesicular eruption; 7 = strong reaction spreading beyond test site.

2.6. Patch adhesion score

Adhesion of the fentanyl patch was assessed immediately after patch application; 12, 24, 36, 48, and 60 h after patch application, and just prior to patch removal. The following adhesion score system was used 0: $\geqslant$90% adhered (essentially no lift off of the skin); 1: $\geqslant$75% to <90% adhered (some edges only lifting off of the skin); 2: $\geqslant$50% to <75% adhered (less than half of the system lifting off of the skin); 3: <50% adhered but not detached (more than half the system lifting off of the skin without falling off), and 4: patch detached (patch completely off the skin).

2.7. Data analysis

The pharmacokinetic parameter estimates of fentanyl were obtained with a non-compartmental analysis approach using WinNonLin, version 5.2 (Pharsight, Mountain View, CA, USA). Calculation of variability was performed according to FDA guidance 3616fnl [21].

The area under the individual fentanyl plasma concentration–time curve up to the last point, at which fentanyl was quantifiable ($AUC_{0\text{-tlast}}$), was estimated using the linear trapezoidal method. Estimates of the apparent terminal elimination rate constant λ_z (identical to k_{el}), were obtained by log-linear least squares regression analysis of the data points which appeared by visual inspection to be on the terminal straight line when plotted on log-linear axes.

The AUC extrapolated to infinity ($AUC_{0\text{-inf}}$) was calculated as the sum of $AUC_{0\text{-tlast}}$ and C_{tlast}/λ_z, where C_{tlast} is the observed fentanyl concentration at time t (t = last). For a calculation of $AUC_{0\text{-inf}}$, the extrapolated area had to be less than 20% of the total AUC. The observed maximum plasma concentration (C_{max}) and the time at which C_{max} occurred (t_{max}) were obtained directly from the measured concentrations.

Intra-subject variability was assessed by treatment. If the absolute difference was more than 100% change in $AUC_{0\text{-inf}}$ or C_{max} between periods within a treatment, the subject (referred to as outlier) was considered as outlier and therefore excluded from the per protocol. The absolute difference was calculated according to the following formula based on non-transformed values of $AUC_{0\text{-inf}}$ and C_{max}.

$$\text{Change}\,\% = \left|\frac{\text{test} - \text{retest}}{\text{mean(test, retest)}}\right|$$

Test and retest related to the two separate periods within the same sequence (ABAB, BABA) when using a particular treatment (either treatment A or B). The mean value was the arithmetic mean of $AUC_{0\text{-inf}}$ or C_{max} of test and retest for each subject. In addition to the per protocol analysis, the 'full analysis set' was also evaluated.

3. Results

3.1. Subjects

A total of 30 healthy, male subjects were enrolled into the study. Their median age was 36 and ranged between 22 and 45 years; body weight (mean ± standard deviation) was 80.1 ± 10 kg. Overall, 28 subjects completed the study according to the study protocol. Due to high-intra-subject differences, two subjects were classified as outliers, and were excluded from the per protocol analysis; per protocol set consisted of 26 subjects.

Sequence ABAB was completed by 15 subjects; sequence BABA was completed by 13 subjects. Two subjects discontinued the study due to adverse events (both subjects) and unwillingness to continue the study (one subject).

3.2. Pharmacokinetics

For both transdermal patch products, all pharmacokinetic parameters of fentanyl from study periods 1–4 determined in this study were similar (Table 1, Fig. 2).

3.3. Analysis of bioequivalence

The summary statistics of pharmacokinetic parameters of fentanyl after 72 h-application periods with the transdermal patch Matrifen® (Test) and Durogesic® DTrans® (Reference) was computed from natural log-transformed data, using a linear mixed effect model with sequence, period and treatment as explanatory factors (Table 2).

The Test/Reference ratios of geometric least squares means (90% CI) of fentanyl were for $AUC_{0\text{-tlast}}$ 92.5 (CI 88.7–96.4), $AUC_{0\text{-inf}}$ 91.7 (CI 88.0–95.7), and C_{max} 98.3 (CI 92.9–104.1), indicating that the two transdermal patches have very similar rate and extent of absorption. Furthermore, the 90% CI of all these pharmacokinetic parameters (per protocol and full analysis set) all were within the range of 80–125%, demonstrating that the fentanyl transdermal patches Matrifen® and Durogesic® DTrans® are bioequivalent (Table 2).

3.4. Intra- and inter-individual variability of pharmacokinetic parameters

Analysis of individual data for the pharmacokinetic parameters C_{max}, $AUC_{0\text{-tlast}}$, and $AUC_{0\text{-inf}}$ showed a lower intra- and inter-subject variability of fentanyl concentration in plasma for Matrifen® than for Durogesic® DTrans® transdermal patch (Table 3).

Table 1
Pharmacokinetic parameter estimates of fentanyl in plasma (per protocol population).

Pharmacokinetic parameter[a]	Fentanyl (100 µg/h)	
	Matrifen® periods 1–4 treatments A_1 & A_2 geometric mean (68% range)	Durogesic® DTrans® periods 1–4 treatments B_1 & B_2 geometric mean (68% range)
Number of treatments	52	52
C_{max} (µg/L)	2.11 (1.42, 3.14)	2.16 (1.34, 3.49)
$AUC_{0\text{-tlast}}$ (µg h/L)	130 (90.1, 187)	141 (91.5, 218)
$AUC_{0\text{-inf}}$ (µg h/L)	133.7 (92.60, 193.0)	146.6 (94.61, 227.1)
k_{el} (1/h)	0.0336 (0.0291, 0.0388)	0.0305 (0.0257, 0.0361)
$t_{1/2}$ (h)	20.62 (17.85, 23.81)	22.75 (19.21, 26.94)
t_{max} (h)[b]	36.00[b] (12.00–84.13)	36.00[b] (12.00–84.00)
AUC_{extrap} (%)	2.5 (1.5, 4.1)	3.1 (1.9, 5.1)

A Matrifen® transdermal fentanyl patch (100 µg/h); A_1 = first application of Matrifen®; A_2 second application of Matrifen®; AUC = area under the concentration–time curve; B Durogesic® DTrans® transdermal fentanyl patch (100 µg/h); B_1 first application of Durogesic® DTrans®; B_2 second application of Durogesic® DTrans®; C_{max} = maximum drug concentration; k_{el} = terminal elimination rate constant; $t_{1/2}$ = plasma elimination half-life; t_{max} = time to maximum concentration.
[a] Patch application period: 72 h. Sampling period for fentanyl concentrations: up to 144 h.
[b] Median (Min–Max).

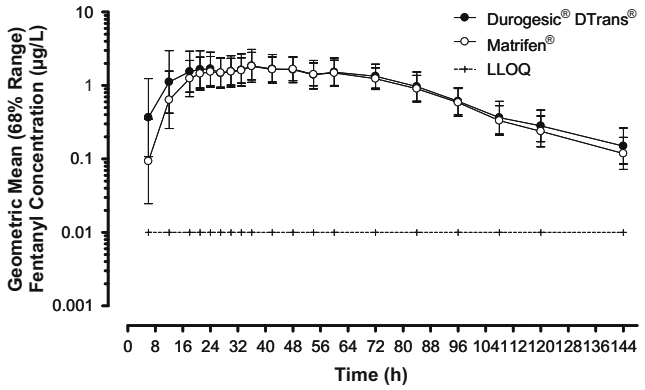

Fig. 2. Plasma concentration–time profiles of fentanyl after application of the transdermal patches Durogesic® DTrans® 100 µg/h and Matrifen® 100 µg/h for 72 h. Geometric mean and 68% ranges for the concentration of fentanyl in the plasma of healthy male subjects. The lower limit of quantitation (LLOQ) for fentanyl is indicated. The transdermal patch Durogesic® DTrans® 100 µg/h (marketed in Germany as Durogesic® SMAT) or Matrifen® 100 µg/h was applied onto the subject's non-dominant upper arm for 72 h. Blood samples for PK analysis were taken for up to 144 h after the patch application. Both transdermal patches were tested on each subject; the washout period between the study periods 1–4 was at least 11 days.

3.5. Drug release and drug utilization

During the 72 h application time, the Matrifen® patch provided a similar rate of drug release as the Durogesic® DTrans® patch (Matrifen® 126 µg/h and Durogesic® DTrans® 122 µg/h). This calculation was based on the amount of fentanyl in individual patches applied, i.e. fentanyl [mg] × 1000/72 h.

The mean initial drug content of the patches applied to the skin of the subjects, calculated from 6 patches per fentanyl preparation, was 38% lower for Matrifen® (mean ± SD value 10.70 ± 0.07 mg) than for Durogesic® DTrans® (mean ± SD value 17.30 ± 0.25 mg). These measured values compare well with the nominal values for the content of fentanyl declared in the 'Summary of the product characteristics' of both products, i.e. 11 mg for Matrifen® [15] and 16.8 mg for Durogesic® DTrans® [14], i.e. 35% lower initial drug content for Matrifen®.

The fact that the Matrifen® patch has a lower original fentanyl drug content (Fig. 3A and B), and that the respective amount of fentanyl delivered to the patients were almost identical between the two different patch systems, indicates that the residual fentanyl in *used* patches after 72 h application (study periods 1–4) was lower in the Matrifen® patch. Consequently, a substantially higher proportion of the original fentanyl drug load was released from the Matrifen® when compared with Durogesic® DTrans® patch (Fig. 3C), allowing an economically and ecologically better utilization of the scheduled administration of the opioid fentanyl.

The mean and median overall delivered dose of fentanyl per subject was similar for Matrifen®: (mean ± SD 9.05 ± 1.04 mg, median 9.32 mg) and for Durogesic® DTrans® (mean ± SD 8.79 ± 2.15 mg, median 8.90 mg) (Fig. 3A). The residual content of fentanyl in the used patches, 72 h after application, was lower in the Matrifen® (mean ± SD 1.95 ± 1.04 mg, median 1.68) than in Durogesic® DTrans® patches (mean ± SD 8.01 ± 2.15 mg, median 7.90 mg) (Fig. 3B), indicating that Matrifen® has a more efficient utilization of fentanyl (mean ± SD 82.3 ± 9.43%, median 84.7%) than Durogesic® DTrans® (mean ± SD 52.3 ± 12.8%, median 53.0%) (Fig. 3C).

Based on the results of the coefficient of variation, the variability for the amount of fentanyl delivered to the subjects was smaller

Table 2
Ratio of pharmacokinetic parameters for the concentration of fentanyl in plasma after application of two different transdermal fentanyl patch formulations (Matrifen® *vs.* Durogesic® DTrans®) (per protocol population).

Parameter estimate[a,d]	Geometric LSM[b]		Ratio[c] %Reference	90% CI
	Test Matrifen®	Reference Durogesic® DTrans®		
$AUC_{0\text{-tlast}}$ (µg h/L)	129.39	139.95	92.5	88.7, 96.4
$AUC_{0\text{-inf}}$ (µg h/L)	133.10	145.08	91.7	88.0, 95.7
C_{max} (µg/L)	2.10	2.14	98.3	92.9, 104.1

AUC = area under the concentration–time curve; CI = confidence interval; C_{max} = maximum drug concentration; LSM = least squares mean.
[a] Patch application period: 72 h. Sampling period for fentanyl concentrations: up to 144 h.
[b] Mixed effect model on natural log-transformed data.
[c] Ratio (Test/Reference) of treatment geometric LSM values, expressed as a percentage of reference geometric LSM (100 × Test/Reference).
[d] The values for the PK parameters did not change substantially when the calculation was performed with all data from all subjects (full analysis set). The resulting data for the 90% CI were all within the predefined range of 80–125%, demonstrating bioequivalence of Matrifen® and Durogesic® DTrans®.

Table 3
Intra- and inter-subject variability of pharmacokinetic parameters of fentanyl in plasma (per protocol population).

Parameter estimate[a]	Inter-subject variability (CV%)		Intra-subject variability (CV%)	
	Matrifen®	Durogesic® DTrans®	Matrifen®	Durogesic® DTrans®
$AUC_{0\text{-tlast}}$ (μg h/L)	37.0	40.6	8.58	13.8
$AUC_{0\text{-inf}}$ (μg h/L)	37.2	41.3	8.47	13.0
C_{max} (μg/L)	37.8	43.4	14.5	17.7

AUC = area under the concentration–time curve; C_{max} = maximum drug concentration; CV = coefficient of variation. The percent coefficient of variation (CV) was calculated according to FDA guideline [21].

[a] Patch application period: 72 h. Sampling period for fentanyl concentrations: up to 144 h.

for the Matrifen® patches than for the Durogesic® DTrans® patches (Table 4, Fig. 3A–C).

3.6. Safety and tolerability

3.6.1. Physical examination

Physical examination and the measurements of body weight, body temperature, 12-lead ECG, and vital signs (blood pressure, pulse rate) revealed no clinically relevant influence of the two tested transdermal fentanyl patches.

3.6.2. Adverse events

During the four study periods, all 30 subjects reported at least one treatment-emergent adverse event (AE). For both patches, all treatment-emergent AEs were of mild to moderate intensity; none was of severe intensity. The number of treatment-emergent AEs was slightly lower during the Matrifen® treatment periods (163 AEs) than during the Durogesic® DTrans® treatment periods (184 AEs). For both transdermal patches, the most frequent treatment-emergent AE was 'skin irritation' occurring in 52% of the treatment periods with Matrifen® and in 46% of the treatment periods with Durogesic® DTrans®.

Other treatment-emergent AEs, selected by frequency, intensity, and medical relevance included headache, abdominal pain, vomiting, and constipation for both transdermal patches and in addition fatigue for Matrifen® and dizziness and nausea for (Durogesic® DTrans®). Two serious AEs were reported for two subjects (ankle fracture, Matrifen®; ligament rupture, Durogesic® DTrans®); none was assessed as related to the use of the transdermal patch.

3.6.3. Patch adhesion

The adhesiveness of both transdermal patches was very good. The individual adhesion scores ranged between 0 (adhesion of $\geqslant$90%) and 2 (adhesion of $\geqslant$50% to <75%). At 72 h after application, the mean ± SD value of the patch adhesion score was 0.5 ± 0.7 for Matrifen® and 0.2 ± 0.5 for Durogesic® DTrans®.

3.6.4. Skin irritation

The results for skin irritation indicate that the skin reactions for both transdermal patches were predominantly mild. The proportion of treatments with 'no evidence of skin irritation' (score = 0) increased between 73 h and 96 h after patch application (corresponding to 1 h and 24 h, respectively, after patch removal). Furthermore, the proportion of treatments with 'no skin irritation' was greater for Durogesic® DTrans® than for Matrifen® at all investigated time points (22% *vs*. 9% at 73 h, 37% *vs*. 17% at 84 h, and 73% *vs*. 50% at 96 h). The highest score was 3 (erythema and papules/pustules) for one treatment with Matrifen® (2%) at 73 h and one with Durogesic® DTrans® (2%) at 96 h.

4. Discussion

The pharmacokinetic profiles of the two different, fentanyl-containing transdermal pain management patches Matrifen® (100 μg/h) and Durogesic® DTrans® (100 μg/h) were compared in normal healthy subjects with regard to the systemic exposure of fentanyl [extent of exposure ($AUC_{0\text{-tlast}}$ and $AUC_{0\text{-inf}}$) and rate of absorption (C_{max})]. The geometric means for all these PK parameters were similar, and their 90% confidence intervals were within the predefined bioequivalence range of 80–125% [21]. Thus, based on these results it can be concluded that the two transdermal matrix delivery systems Matrifen® and Durogesic® DTrans® are bioequivalent.

The nominal values for the surface area and fentanyl content, as declared in the 'Summary of product characteristics', are 33.6 cm^2, 11 mg for Matrifen® [15] and 42 cm^2, 16.8 mg for Durogesic® DTrans® [14]. This corresponds to a difference of 20% in the surface area and 35% in the initial fentanyl content. Despite the difference in the surface area and the initial content of fentanyl, the 72 h application time of the Matrifen® patch provided a similar rate of drug release as the Durogesic® DTrans® patch (Matrifen® 126 μg/h and Durogesic® DTrans® 122 μg/h). The overall dose of fentanyl that diffused to the subjects during this time was also similar for the two transdermal patch preparations. Furthermore, after a 72 h application period, the residual content of fentanyl in the removed (used) patches was lower in the Matrifen® patches, indicating that the efficiency of fentanyl utilization is greater for Matrifen® (Fig. 3B). Based on the adhesion score, both Matrifen® and Durogesic® DTrans® demonstrated excellent and similar adhesive properties at all investigated time points after application (up to 72 h). For Matrifen®, the present results confirm those of previously published studies [16,17]. The variability in the amount of fentanyl delivered into blood circulation (intra- and inter-individual) was lower with Matrifen® than with Durogesic® DTrans®. This could be attributed to the improved matrix technology used in the Matrifen® system, which includes a diffusion rate-controlling membrane [22].

The observed number and intensity of treatment-emergent adverse events, the number of adverse events with causal relationship to the transdermal fentanyl patches, and the respective dermal response scores (skin tolerability after patch removal) were similar between the two tested transdermal patches. For Matrifen®, the type and frequency of adverse events observed in the present study (mild skin irritation) corresponds to previously published studies [16,17].

Apart from demonstrating bioequivalence between the two fentanyl matrix patches and showing that the two transdermal patch formulations have comparable adhesiveness, safety, and skin irritation properties, the data from the present study highlighted several advantages of the Matrifen® patch: first, it delivered the same amount and rate of fentanyl as Durogesic® DTrans®, despite using a 20% smaller patch size; second, it provided a lower drug load; and third, it had a significantly lower residual fentanyl content in the used patches (up to 76% lower). Collectively, these characteristics

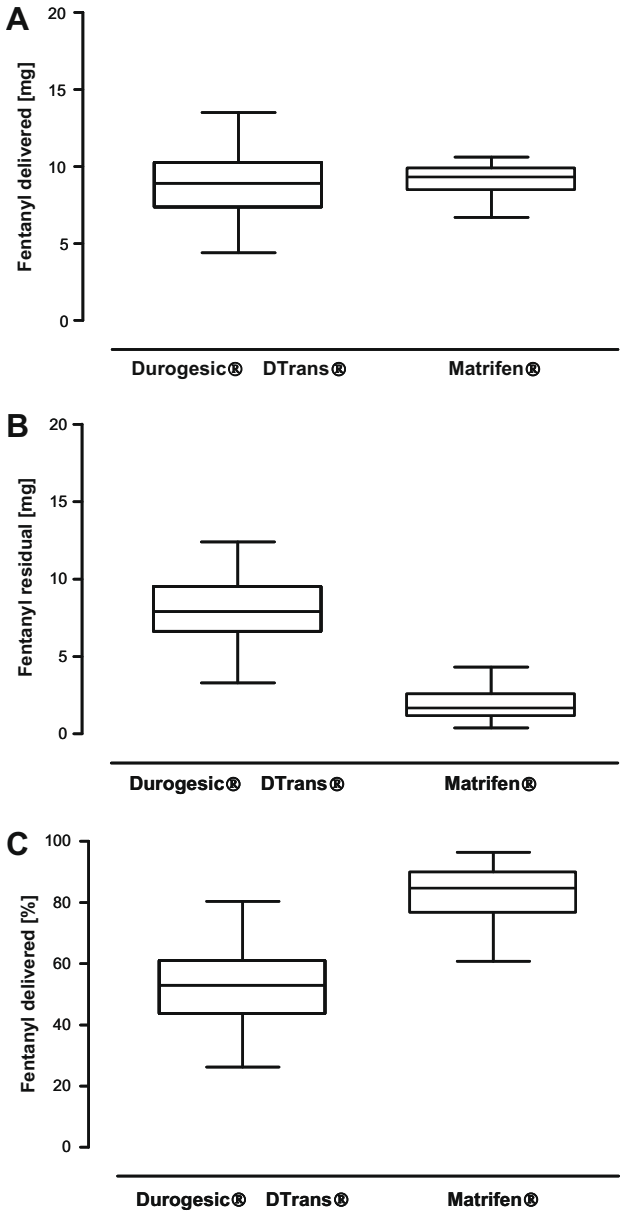

Fig. 3. Comparison of fentanyl delivery to healthy subjects (per protocol population). Comparison of fentanyl delivered from the transdermal patches to the healthy subjects over 72 h (study periods 1–4). The values were calculated from the initial patch drug load nominal values (11 mg for Matrifen® [15] and 16.8 mg for Durogesic® DTrans® (marketed in Germany as Durogesic® SMAT) [14]) and the measured residual fentanyl content in the used transdermal patches. The box–whiskers plots represent the amount of fentanyl in the transdermal patches. The top and bottom line of the box represent the 75th and 25th percentile, respectively; the line inside the box is the median of the data. The ends of the whiskers correspond to the minimum and maximum values. (A) The overall dose of fentanyl delivered per subject for Matrifen® was mean ± SD 9.05 ± 1.04 mg, median 9.32 mg and for Durogesic® DTrans® mean ± SD 8.79 ± 2.15 mg, median 8.90 mg. (B) The amount of residual fentanyl in used transdermal patches for Matrifen® was: mean ± SD 1.95 ± 1.04 mg, median 1.68 mg and for Durogesic® DTrans® mean ± SD 8.01 ± 2.15 mg, median 7.90 mg. (C) The percentage of the drug delivered from the initial patch for Matrifen® was: mean ± SD 82.3 ± 9.43%, median 84.7% and for Durogesic® DTrans® mean ± SD 52.3 ± 12.8%, median 53.0%.

indicate that Matrifen® patch can provide a constant and efficient utilization of the fentanyl drug (Fig. 3A–C) [14,15].

In conclusion, for the transdermal patches Matrifen® and Durogesic® DTrans®, all investigated PK parameters of fentanyl were similar and within the predefined bioequivalence range. These results demonstrate that the two products are bioequivalent and can be expected to have similar efficacy for pain management in a clinical setting [3,12].

Table 4
Variability of fentanyl delivered to the subjects (per protocol population).

Transdermal patch	Study period	Mean (mg)	SD (mg)	CV (%)
Matrifen® 100 μg/h	1	8.46	1.04	12.4
	2	8.10	0.69	8.47
	3	9.93	0.45	4.51
	4	9.66	0.42	4.34
	All periods	9.05	1.04	11.5
Durogesic® DTrans® 100 μg/h	1	7.95	2.10	26.4
	2	8.66	2.29	26.5
	3	9.06	2.04	22.6
	4	9.41	2.11	22.4
	All periods	8.79	2.14	24.5

SD = standard deviation; CV = coefficient of variation.
Mean values (mg), standard deviation (SD) (mg), and percent coefficient of variation (CV) of fentanyl delivered into the circulation of healthy subjects. The values were calculated separately for each of the study periods 1–4. Calculations are based on the nominal initial amount of fentanyl in the transdermal patches and on the residual content of the patches after 72 h application. The term 'All periods' represents the values for all patches (irrespective of the period) for either Matrifen® or Durogesic® DTrans®.

Acknowledgements

The authors thank Dr. Kathy B. Thomas (formerly of Nycomed GmbH, Konstanz, Germany) for valuable suggestions during the preparation of the manuscript.

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